REMARKS/ARGUMENTS

For the purpose of advancing prosecution, claims 21 and 45 have been amended to recite a pharmaceutical composition "for the reduction of pain upon injection." Support for this amendment resides throughout the specification, for example, at page 4, lines 1-8, page 6, lines 21-26, and Example 4 at page 26. No new matter is added by way of claim amendment. The Examiner is respectfully requested to enter these claim amendments into the above-referenced application.

Claims 21-34, 45, and 46 are pending in the application. Reexamination and reconsideration of the claims is respectfully requested in view of these amendments and the following remarks. The Examiner's comments in the non-final Office Action are addressed below in the order set forth therein.

The Rejection of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 21-34, 45, and 46 stand rejected under 35 U.S.C. §103(a) as being obvious in view of Clark *et al.* (U.S. Patent No. 5,597,802; hereinafter the '802 patent). This rejection is respectfully traversed for all of the reasons of record and further in view of the following remarks.

Applicants' claimed invention is directed to pharmaceutical compositions that are formulated to reduce pain upon injection. Applicants are the first to discover the added benefit of reduced pain upon injection of succinate-buffered IGF-I when formulated with succinate at the recited concentration range. This added benefit could not have been predicted from the prior art patent serving as the basis of this obviousness rejection.

To the contrary, as Applicants have made of record, the '802 patent teaches a preferred composition for formulating IGF-I and growth hormone, i.e., one that utilizes an acetate buffer to maximize stability of these proteins. This preferred composition thus uses a buffer that results in much greater pain upon injection, as evidenced by Applicants' data provided in Example 4 and Figure 7, and substantially greater inflammation at the injection site, as evidenced by Applicants' data provided in Example

5. Accordingly, the teachings of the '802 patent, when taken as a whole, lead one of skill in the art to formulate IGF-I and/or IGF-I + GH in a manner that is contrary to the objective recited in Applicants' claimed invention, wherein IGF-I or variant thereof is formulated for reduced pain upon injection.

The Office Action asserts that the teaching of a preferred composition in the '802 patent "does not exclude other embodiments (i.e., succinate, citrate, pH 6.0) in the genus" (Office Action mailed September 29, 2006, last sentence of page 5 continuing through line 1 of page 6). Applicants respectfully note that their arguments of record are not intended to "exclude other embodiments." Rather, Applicants have merely requested that the Examiner properly consider the teachings of '802 patent *as a whole*, as is legally required in establishing rejections under Section 103.

In that regard, Applicants note that succinate is mentioned only twice within this patent: at column 11, line 45, in the context of a long list of pharmaceutical carriers, and at column 13, lines 16-24, in the context of a Markush grouping of GRAS buffers that can suitably be used to practice the '802 invention. In contrast, no less than seven times in the "Description of Preferred Embodiments" section of the '802 patent, an acetate buffer is referred to as the buffer to be used in formulating IGF-I and/or IGF-I + GH. In addition, all of the experimental data (see particularly Examples V-XIII) demonstrate the desirability of formulating IGF-I, with or without GH, at pH 5.0 or 5.4 with sodium acetate buffer in order to maximize the potency and efficacy of this protein when injected into an animal.

This patent provides no guidance whatsoever to lead one of skill in the art to formulate IGF-I or variant thereof in the recited range of succinate buffer that Applicants have discovered provides reduced pain upon injection relative to other commonly used buffers. To the contrary, where the inventors of the '802 patent stress the desirability of formulating IGF-I at pH 5.0 to 5.5, and further demonstrate the suitability *and the pronounced biological advantage* of formulating this protein at that pH range using sodium acetate buffer, there is no motivation whatsoever to modify this reference to formulate IGF-I with a succinate buffer, particularly at pH 6.0, and particularly at the concentration ranges recited in Applicants' claimed invention.

Applicants respectfully submit that the '802 patent teaches a buffer concentration of about 5 to 100 mM for increased stability of a preferred IGF-I+GH formulation, which the experimental data clearly demonstrates is a composition comprising sodium acetate buffer. While succinate is listed within a Markush grouping of suitable GRAS buffers, its suggestion is at most an invitation to experiment; there is no guidance to lead the skilled artisan to the succinate concentration range recited in Applicants' claimed invention that provides for reduced pain upon injection. The surprising finding that pain upon injection could be reduced by utilizing a particular buffer at a particular concentration was not obvious. Given the laundry list of buffers generically disclosed for use in practicing the invention of the '802 patent, and the broad concentration range of buffer disclosed in the context of a preferred IGF+GH formulation, one of ordinary skill in the art would not have a reasonable expectation of success in selecting the concentration ranges of the succinate buffer utilized by Applicants to reduce pain upon injection.

The Office Action asserts that Applicants' arguments regarding no reasonable expectation of success are not persuasive. The Examiner reasons this is so because "this concentration range is commonly used for preparing buffers in a composition, where reducing pain during rejection [*sic*] is an issue" (Office Action mailed September 29, 2006, at page 6, lines 1-6). Applicants respectfully disagree.

The only cited prior art at issue is the '802 patent. This patent makes no mention of the problem of pain upon injection of IGF-I-containing buffered formulations. The Examiner has not cited to any prior art publication showing that IGF-I formulated in succinate buffer would be expected to have less pain upon injection. Applicants respectfully submit that the motivation to formulate IGF-I in the manner recited in the pending claims is provided by Applicants' disclosure, not the teachings of the prior art.

As such, this obviousness rejection appears to be a case of hindsight reasoning, where Applicants' specification has been used as a blueprint to reach the claimed invention from the cited prior art disclosure. Yet the law requires that the suggestion to modify the teachings of the prior art and the expectation of success must be found in the prior art itself, not in Applicant's disclosure. *In re Dow Chemical*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) (reversing the PTO's

conclusion of obviousness). Furthermore, with regard to the sole reference within the '802 patent to a concentration range for a buffer, Applicants note that "[a] single line in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness." *Bausch & Lomb, Inc. v. Barnes Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 USPQ 416, 419 (Fed. Cir. 1986).

Applicants respectfully submit that this obviousness rejection is predicated on two statements within the '802 patent, i.e., the inclusion of succinate as a member within the Markush grouping of GRAS buffers, and the disclosure of a concentration range of about 5 to 100 mM of a buffer to be included in a preferred embodiment of the '802 invention. Yet these statements have been taken out of context and combined to reach Applicants' claimed invention, wherein Applicants' specification has provided the motivation to do so. This is clearly contrary to the accepted legal standard for obviousness rejections. *See*, for example, *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000), stating:

> While the test for establishing an implicit teaching, motivation, or suggestion is what the combination of . . . two statements of a [prior art reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, *with no knowledge of the claimed invention*, would have selected these components for combination in the manner claimed [emphasis added].

See also, *In re Wesslau*, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965), stating, "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art"; and *In re Mercer*, 515 F.2d 1161, 1165-66, 185 USPQ 774, 778 (CCPA 1975).

As the Examiner is well aware, hindsight reconstruction is an impermissible standard upon which to make an obviousness determination. *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (ruling that it is impermissible to use the claimed invention as an instruction manual

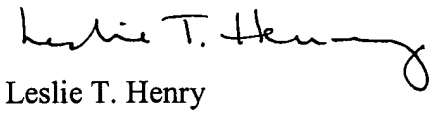
or template to piece together the teachings of the prior art to render it obvious). Accordingly, for this and all of the reasons made of record, Applicants maintain that this obviousness rejection should be withdrawn.

CONCLUSION

In view of the aforementioned claim amendments and remarks, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. §103 is overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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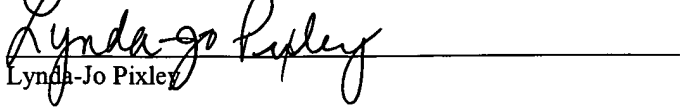

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